REMARKS

I. Status of the Application and Claims:

With entry of this amendment, Claims 1-3, 5-7, 9, 20-24, 28, and 29 are pending in the application. Those claims have been examined on the merits and stand rejected.

Applicants have canceled withdrawn claims 8, 10-19, and 25-27 without prejudice or disclaimer of the subject matter recited therein, as required. *See,* Office action, page 10. They reserve the right to pursue the canceled subject matter in one or more divisional applications.

Applicants have also canceled claim 4. The language of the canceled claim appears in amended claim 1.

Applicants have amended claim 20 to delete reference to canceled claim 15, and amended claims 5 and 6 to change the claim from which they depend. The amendments does not introduce new matter.

The Office has objected to claim 3 because it contains a typographical error. *Id.*, page 2. Applicants have amended the claim as suggested by the Office. They request reconsideration and withdrawal of the objection.

II. Amendment of the Specification to Correct an Obvious Error

Applicants have amended the specification to correct an obvious typographical error. Specifically, at page 7, line 20, Applicants have amended the reference to "96 amino acids" to correctly recite "196 amino acids." Support for the amendment is found in the paragraph containing the amendment. As disclosed in that paragraph, the third intracellular loop ["IC3"] of the wild type M3 MAR consists of 240 amino acids. Specification, page 7, lines 23 and 24. The specification also teaches that as a consequence of the IC3Δ deletion, there are 44 amino acids remaining in the IC3.

Twenty-two of those amino acids are proximal to the 5th transmembrane helix and twenty-two are proximal to the 6th transmembrane helix. *Id.*, lines 21-23. If there are 240 amino acids in the wild-type IC3, and 44 amino acids remain after the deletion mutation, then 196 amino acids must have been deleted. This is confirmed by the statement in the specification that amino acids Ala273-Lys469 were deleted. That span consists of 196 amino acids (469 – 273 = 196).

Thus, the sentence in the specification at line 20-22 stating that "[t]he bulk of this domain, 96 amino acids in the center of the IC3 (Ala273-Lys469), were deleted, leaving only 22 amino acids proximal to both the 5th and 6th transmembrane helices[ ]" contains an obvious typographical error. One of skill in the art, reading this paragraph of the specification, would not only recognize that "96 amino acids" is in error, but also recognize from the specification that the appropriate correction is "196 amino acids," as indicated in the amendment. The amendment to correct this obvious error does not constitute new matter. *See* M.P.E.P. § 2163.07, *citing In re Oda*, 170 U.S.P.Q. 268 (C.C.P.A. 1971). Accordingly, Applicants request entry of the amendment.

III. Claim 29 Is Definite and Unambiguous

The Office maintains the rejection of claim 29 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter Applicants regard as their invention. Office action, page 3. Applicants traverse the rejection.

Applicants have pointed to the teaching of the specification at page 7, lines 19-24, as providing meaning for "IC3Δ" as recited in claim 29. In reply to Applicants' reliance on that teaching, the Office states that "[t]he parenthetical reference of the 44

amino acid deletion referred to by applicant does not establish that the claim is limited to this particular deletion." *Id.* Applicants respectfully disagree with the Office's interpretation of this passage:

> The IC3, found between 5th and 6th membrane spanning helices, was the only domain modified. The bulk of this domain, [[96]] 196 amino acids in the center of the IC3 (Ala273-Lys469), were deleted, leaving only 22 amino acids proximal to both the 5th and 6th transmembrane helices. Thus, the third intracellular loop of the MAR containing the IC3 deletion (IC3Δ) is 44 amino acids in length, compared to 240 amino acids in the IC3 of wild type M3 MAR.

Specification, page 7, lines 19-24; as amended herein.

The quoted passage does not, as the Office reads it, refer to a 44 amino acid deletion. It refers to a 196 amino acid deletion of amino acids Ala271-Lys469 of the IC3. That deletion leaves behind 44 amino acids of the IC3: (1) the 22 amino acids proximal to the 5th transmembrane helix; and (2) the 22 amino acids proximal to the 6th transmembrane helix. Thus, the meaning of "IC3Δ" is clearly and unambiguously set forth in the specification.

The Office cites generally to page 3 of the specification as supporting the ambiguity of "IC3Δ." Respectfully, Applicants fail to understand how any of the disclosure on page 3 obfuscates the clear teaching on page 7, and they respectfully request that the Office identify the specific disclosure it believes supports the rejection.

In view of these remarks, Applicants request that the Office reconsider and withdraw the rejection of claim 29 under section 112, second paragraph.

III. The Cited References Do Not Anticipate the Claims

A. Sledziewski

The Office maintains the rejection of claims 1 and 20 under 35 U.S.C. § 102(b) as allegedly anticipated by U.S. Patent No. 5,576,210 to Sledziewski *et al.* ("Sledziewski"). Office action, page 3. Applicants traverse.

Applicants have amended claim 1 to recite the language of now canceled claim 4, which was not subject to this rejection. Claim 1, and dependent claim 20, therefore, are not anticipated by Sledziewski because, as in the case of canceled claim 4, that reference does not teach (or suggest) all of the limitations of the rejected claims. For that reason, Applicants request that the Office reconsider and withdraw the rejection.

B. Fowlkes

Claims 1-7, 20-24, 28, and 29 remain rejected under 35 U.S.C. §§ 102(a) and (e) as allegedly being anticipated by U.S. Patent No. 5,789,184 to Fowlkes *et al.* ("Fowlkes"). Office action, page 4. The rejection is moot as to canceled claim 4. Applicants traverse the rejection for the reasons of record, supplemented as follows.

Other than with respect to the passage at col. 26, lines 19-25, Applicants and the Office continue to disagree concerning the teaching of Fowlkes that the Office specifically cites in making the rejection. According to the Office, col. 15, lines 29-63, of Fowlkes teaches that the mutated GPCR disclosed in col. 26, lines 19-25 "has been modified as a matter of routine optimization of operating parameters, i.e. such that it is improved in its functions in a cell based assay as compared to wild-type." Office action, page 4. The cited passage, taken from a section of the specification defining certain terms, recites the following:

The PSP surrogate may be a protein which must be modified in some way by a drug to be functional. For example, the drug could cause an allosteric change in the PSP surrogate's conformation, or it could cleave off a portion of the surrogate, the balance of the protein then being a functional molecule.

The PSP surrogate may also be one which is functional only if other modifications are made in the yeast cell, e.g., expression of a chimeric G α subunit to interact with an exogenous G protein-coupled receptor.

The term "substantially homologous" when used in connection with amino acid sequences, refers to sequences which are substantially identical to or similar in sequence, giving rise to a homology in conformation and thus to similar biological activity. The term is not intended to imply a common evolution of the sequences.

Typically, "substantially homologous" sequences are at least 50%, more preferably at least 80%, identical in sequence, at least over any regions known to be involved in the desired activity. Most preferably, no more than five residues, other than at the termini, are different. Preferably, the divergence in sequence, at least in the aforementioned regions, is in the form of "conservative modifications."

"Conservative modifications" are defined as

(a) conservative substitutions of amino acids as hereafter defined; and

(b) single or multiple insertions or deletions of amino acids at the termini, at interdomain boundaries, in loops, or in other segments of relatively high mobility.

Preferably, except at the termini, no more than about five amino acids are inserted or deleted at a particular locus, and the modifications are outside regions known to contain binding sites important to activity.

Fowlkes, col. 15, lines 29-63.

Applicants respectfully request that the Office identify with particularity the language in the quoted passage that it contends is a teaching of a GPCR that "has been modified as a matter of routine optimization of operating parameters, i.e. such that it is improved in its functions in a cell based assay as compared to wild-type." Applicants,

for their part, fail to see how any section of the quoted language leads to the conclusion the Office has reached.

In reply to Applicants' arguments, the Office states that "[o]ne of ordinary skill in the art would ask what other reason would Fowlkes teach conservative mutations in the receptor other than to improve the function, i.e., the coupling of the receptor to the G-protein, as this is the very essence of the assay." Office action, page 4. Applicants submit there may be many reasons for introducing mutations into a protein sequence, for example, to improve the expression, processing, or stability of the protein. It is not necessarily the case that a mutation is introduced to improve a protein's function. Regardless, there is no express teaching in Fowlkes that the "conservative mutations" mentioned generally in col. 15 are mutations that "improve[e] the function of said heterologous G protein-coupled receptor by causing it to couple more efficiently with a heterotrimeric G protein compared to a wild-type form of the heterologous G protein-coupled receptor . . ." as recited in the claims.

Applicants and the Office also disagree over the teaching of col. 10, lines 27-44. The Office contends that passage teaches "the functionality of the modification [to the GPCR] is clearly taken to be an improvement in the agonist-induced growth of the cells." Office action, page 4. In reply to Applicants' arguments, the Office states that "[b]y referring to col 10, L27-44, the examiner is simply citing were [*sic*, where] it is understood that the function of the receptor, and thus the modification to it, is clearly taken to be an improvement in the agonist-induced growth of the cells." *Id.*, pages 4 and 5. The cited passage states:

> However, when searching for peptides which can function as agonists of G protein-coupled receptors, or other pheromone system

> proteins, the growth arrest consequent to activation of the pheromone response pathway is an undesirable effect for this reason: cells that bind peptide agonists stop growing, while surrounding cells that fail to bind peptides will continue to grow. the cells of interest, then, will be overgrown or their detection obscured by the background cells, confounding identification of the cells of interest. To overcome this problem, the present invention teaches engineering the cell such that: 1) growth arrest does not occur as a result of pheromone signal pathway activation (e.g., by activating the FAR1 gene); and/or 2) a selective growth advantage is conferred by activating the pathway (e.g., by transforming auxotrophic mutant with a HIS3 gene under the control of a pheromone-responsive promoter, and applying selective conditions).

Fowlkes, col. 10, lines 27-44.

FAR1 is a cyclin-dependent kinase inhibitor. HIS3, which permits cell growth on medium lacking histidine, is used as a reporter gene. Neither gene is a G protein-coupled receptor. Applicants respectfully request that the Office explain how the quoted passage supports the assertions found on pages 4 and 5 of the Office action.

Applicants maintain their position that nothing in this passage teaches or suggests "the functionality of the modification is clearly taken to be an improvement in the agonist-induced growth of the cells . . . ." Instead, this section mentions the undesirable growth arrest consequence of activating the pheromone response pathway and identifies two ways of overcoming that problem. None of those ways involve introducing the mutation recited in the claims into a heterologous G protein-coupled receptor.

For all of these reasons, Applicants submit that Fowlkes does not teach (or suggest) each and every limitation of the rejected claims. Because it fails to do so, the Office should reconsider and withdraw the rejection.

IV. The Cited References Do Not Render the Claims Obvious

A. Sledziewski and King

Claim 2 has been rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Sledziewski in view of PCT application WO 92/05244 to King *et al.* ("King"). Office action, page 5. Applicants traverse the rejection because the references do not render the claims *prima facie* obvious in that they fail to teach or suggest all of the limitations of the rejected claim. Furthermore, in view of the teaching of Strader, the prior art as a whole, which the Office must consider, does not provide a teaching, suggestion, or motivation to combine the references, nor a reasonable expectation of success.

Applicants have discussed the teaching of Sledziewski and its deficiencies. Sledziewski teaches mammalian/yeast hybrid GPCRs. That reference does not teach or suggest "[a] yeast cell comprising a nucleic acid sequence encoding a mutated, heterologous G protein-coupled receptor, wherein the mutation is a deletion mutation in an intracellular domain of the G protein-coupled receptor . . ." as recited in claim 2. The teaching of King does not cure that deficiency. King is merely cited as teaching an assay where the effect of an agonist would be to induce HIS3, which is used to produce agonist-induced growth of cells. *Id.*, page 5.

The teaching of King, however, does not cure the deficiency in the teaching of Sledziewski. The combination of Sledziewski and King does not teach or suggest a "mutated, heterologous G protein-coupled receptor, wherein the mutation is a deletion mutation in an intracellular domain of the G protein-coupled receptor . . . ." The combination of Sledziewski and King, therefore, does not teach or suggest all of the

limitations of rejected claim 2. For that reason, claim 2 is not *prima facie* obvious over that combination of references

In addition, one of skill in the art would not have been motivated to combine the references, nor have a reasonable teaching of success in view of the teaching of Strader. The Office has admitted that "Strader teaches away from the expectation that such deletions would improve functional coupling of the receptor to the G protein." Office action mailed February 10, 2004, page 5. In the instant action, the Office attempts to distance itself from its understanding of the art, on several grounds.

First, the Office notes that Strader is not being relied on in the instant rejection. Office action, page 6. Respectfully, whether or not the Office relies on a reference is irrelevant because the prior art as a whole must be considered when analyzing the patentability of claims under section 103. The Office may not dismiss Strader's teaching because it does not rely on that reference in rejecting the claim.

Second, the Office states that "the examiner's statement was merely intended to provide a road map to overcoming the rejection based on Strader" and that "[t]he results of Strader simply point out the great diversity and adaptability of GPCR assays." Office action, page 6. The Examiner's intent when characterizing the state of the art is not relevant. What is relevant is the characterization of the art. Here, Strader's teaching has been clearly and unambiguously set forth by the Office as "teach[ing] away from the expectation that such deletions would improve functional coupling of the receptor to the G protein." It is difficult to reconcile the Office's initial interpretation of Strader with its subsequent assertion that Strader points out the great diversity and adaptability of

GPCR assays. For these reasons, Applicants submit that the teaching of Strader is further evidence showing the unobviousness of claim 2 over the cited references.

For all of these reasons, Applicants submit that claim 2 is not *prima facie* obvious over the combination of Sledziewski and King. They request reconsideration and withdrawal of the rejection.

B. Sledziewski and Bonner

The Office maintains the rejection of claim 9 under 35 U.S.C. § 103(a) as allegedly unpatentable over Sledziewski in view of Bonner *et al.*, Science, 237:527-537 (1987) ("Bonner"). Office action, page 6. Applicants traverse the rejection for the reasons of record, supplemented as follows.

Applicants have discussed the teaching of Sledziewski and its deficiencies. Bonner is only cited for its teaching of the rat M3 muscarinic receptor. *Id.* The teaching of Bonner does not cure the deficiency in the teaching of Sledziewski, which Applicants have noted above. Therefore, the combination of Sledziewski and Bonner does not teach or suggest all of the limitations of claim 9, which recites a "mutated, heterologous G protein-coupled receptor, wherein the mutation is a deletion mutation in an intracellular domain of the G protein-coupled receptor . . . ." For that reason, claim 9 is not *prima facie* obvious over the combination of Sledziewski and Bonner.

In addition, for the reasons discussed above, one of skill in the art would not have been motivated to combine the references, nor have a reasonable expectation of success, in view of the teaching of Strader.

Accordingly, Applicants submit that claim 9 is not *prima facie* obvious over Sledziewski and Bonner. They request reconsideration and withdrawal of the rejection.

C. Fowlkes and Bonner

Claim 9 also remains rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Fowlkes in view of Bonner. Office action, page 7. Applicants traverse.

Applicants have discussed the teaching of Fowlkes and its deficiencies. Bonner is cited for its teaching of the rat M3 muscarinic receptor. As in the case of the combination of Sledziewski and Bonner, the combination of Fowlkes and Bonner does not cure the deficiency in the teaching of the primary reference Fowlkes. The combination of Fowlkes and Bonner, therefore, does not teach or suggest all of the limitations of the rejected claim. For that reason, claim 9 is not *prima facie* obvious over that combination of references.

In addition, for the reasons discussed above, one of skill in the art would not have been motivated to combine the references, nor have a reasonable expectation of success, in view of the teaching of Strader.

Accordingly, Applicants submit that claim 9 is not *prima facie* obvious over Fowlkes and Bonner. They request reconsideration and withdrawal of the rejection.

V. The Specification Enables the Full Scope of Claim 13

Claim 13 remains rejected under 35 U.S.C. § 112, first paragraph, "because the specification, while been enabling for a modification that results in a 44 amino acid third intracellular loop comprising the 22 residues proximal to the 5th and 6th transmembrane domains," allegedly "does not reasonably provide enablement for all other modifications resulting in a 44 amino acid third intracellular loop . . . ." Office action, page 8. Applicants traverse for the reasons of record.

Solely to expedite prosecution, however, Applicants have canceled claim 13. Accordingly, the rejection is moot, and Applicants request that the Office withdraw it.

CONCLUSION

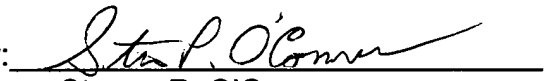
In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and reexamination of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.

Dated: January 6, 2004

By: 

Steven P. O'Connor
Reg. No. 41,225
571.203.2718